DISSERTATION

Pattern of Endocrine Causes of short stature among children, 2 to 12 years of age in an urban referral centre

Submitted in fulfilment of requirements for the degree of M.D. Paediatrics

BRANCH VII

THE TAMILNADU Dr. MGR MEDICAL UNIVERSITY

CHENNAI

APRIL 2012

INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN

EGMORE, CHENNAI.

CERTIFICATE

This is to certify that the dissertation titled "ETIOLOGICAL AND CLINICAL PROFILE OF SHORT STATURE" is an original work done by Dr.D.SURESH in the Department Paediatric Endocrinology ,Institute Of Child Health and Hospital For Children Egmore,Chennai-600008 and has been done under guidance and supervision during the period of his post graduate study for M.D.(Branch VII)Paediatrics.

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Declaration

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This is submitted to the Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulations for the M.D. Degree Examinations in Paediatrics.

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SPECIAL ACKNOWLEDGEMENT

My sincere thanks to **Prof. Dr.V.Kanagasabai, M.D., Ph.D, D.N.B.,** Dean, Madras Medical College, Chennai for permitting me to utilize the clinical materials of the hospital for the successful execution of my study.

ACKNOWLEDGEMENT

At the outset I would like thank our beloved Director and superindentant of this Institute of child health and health for children, Egmore , chennai , Prof . Dr. J. Jayachandran for giving me this golden oppurtunity to do this study.

I thank our beloved,dedicated and esteemed Prof.Dr.S.Sundari MD DCH, Additional Professor of paediatrics,for invaluable guidance, constant support and encouragement given by her in every aspect of this study.

I thank my great teacher Asst. Prof.Dr.S.Lakshmi MD.,for her remarkable expertise knowledge in guiding me for this work to be done. I have completed this work because of her constant guidance, keen interest and constructive criticism.

I express my sincere thanks and gratitude to Dr.C.V.Ravisekar MD DCH DNB, Dr. S .Lakshmi MD DCH, Dr.K.Kumarasamy MD DCH and Dr.Karamath MD for their meticulous supervision and invaluable guidance in preparing this dissertation without whom I would never have been able to gather and compile these materials.

I wish to pay humble regards and thanks to my respectful teacher Dr.K.Nedunchelian Assistant Professor whose concern, enthusiasm and everlasting quest to complete this study.

I express my sincere thanks to Mr. Periyannan, Professor of Epidemiology for his help and advice.

I express my heartful thanks to all children who participated in the study and their parents for their consent and continuous cooperation during this study.

I owe my thanks to my parents,family and friends who helped me in completing this study successfully.

I thank everyone whom I could not mention here, but have directly or indirectly supported me throughout this study.

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The Institutional Review Board [Ethical committee] of Institute of Child Health and Hospital for Children, Chennai-08, was held on 30.01.2010 at 10.00AM at the Deputy Superintendents chamber.

Members Present: Dr.R.Kulandai Kasthuri
Chair Person.

Members:
1. Dr.K.Gita
2. Dr.P.Jeyachandran
3. Dr.D.Vijaya Sekaran
4. Prof.Girija Shyam Sundar
5. Mrs.Muthu Lakshmi, (Advocate)
6. Dr.P.Ramachandran
7. Mrs.Shubha Kumar

Member Secretary: Dr.Luke Ravi Chellaiah

Title: "Pattern of Endocrine Causes of Short Stature among Children, 2-12 years of age in an Urban Referral Centre".

The Institutional Review Board was satisfied with the revised format submitted by you. Hence the Institutional Review Board is pleased to approve the study.

To,
Dr.D.Suresh,
Post Graduate,
ICH & HC,
Chennai-08.

Director and Superintendent.

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INTRODUCTION

Normal growth:

Growth can be defined as a process of increase in size by accretion of tissue. It is observed in the whole organism, in body regions, in organ systems, and in the cellular environment. Human growth starts at conception and proceeds through various identifiable developmental stages. It is dependent on cell hyperplasia (an increase in cell number), cell hypertrophy (an increase in cell size) and apoptosis (programmed cell death). Hyperplasia and apoptosis are genetically regulated to limit the size of an organ or the body.

The process of growth is complex. The process of growth depends on both genetic and environmental factors that combine to determine an individual's eventual height.

The genetic control of statural growth is becoming increasingly clear. Many genes have been identified that are required for normal development and function of the pituitary and that control the growth hormone/insulin-like growth factor axis in particular. So every child grows normally in predictable manner. Hence longitudinal assessment of all children's growth is essential for all paediatric practice. The

most common referral to paediatric endocrinologist is a concern of growth failure.

Definition:

A child is considered to be short when his /her height is below the 3rd centile on a height chart for the specific population . It is important to use country specific updated growth charts so that appropriate population standards are applied and over diagnosis of short stature is avoided. While using growth charts, parents' heights should be considered and adjusted midparental height (MPH)(sex Specific target height)should be plotted.

Factors affecting human growth:

Linear growth of an individual and final adult height is determined by his/her genetic potential. However true realization of one's growth potential depends upon general well being, nutrition and hormonal mileu like growth hormone, thyroid hormone, insulin like growth factor 1,2, $IGFBP_{3.}$

From weeks 4 to 8, there is rapid growth and differentiation to form all the major organ systems in the body. In the second trimester,

the fetus undergoes major cellular hyperplasia and in the third, organ systems mature in preparation for extrauterine life.

Throughout gestation, fetal growth is constrained by maternal factors and placental function but is co-ordinated by growth factors [2]. These can act locally in a paracrine manner [eg. IGF-I and IGF-II, fibroblast growth factor, epidermal growth factor, transforming growth factors α and β] or as endocrine hormones (e.g. insulin). Nutrition from the mother plays a rate-limiting role.

During the first year, infants grow rapidly but at a sharply decelerating rate [1,3]. A similar pattern is observed for weight gain. It has been postulated that nutritional input is the principal regulator of growth over this period with minimal contribution from growth hormone.

Data from humans and transgenic animal models suggest that the hormones and receptors within the GH–IGF axis also play their part in this early phase of growth. Nevertheless, it is during this period that alterations in dietary intake are likely to have the greatest impact on growth. Although growth charts give the impression that growth is linear, most studies of short-term growth (day to day, week to week) find it to be non-linear [4].

By 4 years of age, average growth velocity has declined to 7 cm/year and remains relatively steady until adolescence, the prepubertal nadir in average velocity being 5 to 5.5 cm/year. On an individual basis, there is a well-recognized mid-childhood growth spurt. Additionally, if an individual is measured throughout childhood, oscillations in growth velocity of variable amplitude are observed With a periodicity of approximately 2 years [5].

During childhood, growth hormone, in addition to thyroid hormone, is the major determinant of growth. It is therefore the time when dysfunction in the GH axis may be recognized. There is also wide variation in pubertal timing within each sex. The later onset of puberty in boys gives them two additional years of prepubertal growth compared with girls.

The height gained in this time (8–10 cm), in addition to the greater amplitude of pubertal growth in boys (3–5 cm more than the female growth spurt), gives rise to the 12.5 cm difference in adult height between the sexes.

Constitutional delay of growth and puberty is common and can be considered a variant of normal. The condition can be associated with chronic disease, for example atopy, but more often occurs in isolation. Pubertal development commences late and the growth spurt

is blunted. Although constitutional delay in growth and puberty may actually present in the pubertal years, some children may have shown slow growth much earlier in childhood. The corollary is constitutional tall stature and early puberty, which is associated with more intense pubertal growth than normal. The net result is that both early and late maturers should achieve a comparable height.

The degree of physical development and the timing of the pubertal growth spurt complicate assessment of growth velocity around puberty[6]. It is this variation that gives rise to the wide variation in peak height velocity on growth charts.

The endocrine control of growth:

The principal hormones influencing growth are GH and the IGFs, but there are many other hormones that contribute, including thyroid hormones, adrenal androgens, sex steroids, glucocorticoids, vitamin D, leptin, and insulin. Often, this contribution is channeled through interaction with the GH–IGF axis.

Hypothalamic control of GH secretion:

Growth hormone is secreted from the anterior pituitary in discrete pulses every 3–4 hr, with very low concentrations of growth hormone present between pulses. This pattern is determined by the interaction between growth hormone-releasing hormone, ghrelin and somatostatin[7].

The amplitude of the GH peak is determined by GHRH. Ghrelin acts in synergy with GHRH to promote GH release. Ghrelin also has a potent orexigenic action, indicating a link between nutritional and growth control. Withdrawal of somatostatin is the most important factor in determining the time of a pulse as GH pulsatility is maintained under constant infusion of GHRH.

Pituitary control of GH secretion:

The human GH gene forms part of a cluster of five similar genes found on the long arm of chromosome 17 [7]. The main form of GH in the circulation comes from the GH-N (or normal) gene expressed primarily in the pituitary. The full-length transcript from the GH-N gene encodes a 191-amino-acid, 22 kDa protein, which constitutes 80–90% of pituitary GH. Alternative splicing of the mRNA

transcripts generates a 20 kDa species that lacks amino acids 32–46 and accounts for the remaining 10–20%. Deletion of the GH-N gene in humans leads to severe postnatal growth failure and in these individuals; treatment with GH generates a short-lived growth response resulting from the development of anti- GH antibodies.

Other factors influencing GH secretion:

Table 8. Physiologic factors that affect GH secretion.

Factors that stimulate GH secretion	Factors that suppress GH secretion
Exercise	Hypothyroidism
Stress	Obesity
Hypoglycemia	Hyperglycemia
Fasting	High carbohydrate meals
High protein meals	Excess glucocorticoids
Sleep [7]	

Growth hormone in the circulation:

Serum levels of GH rise to high levels by 24 weeks of gestation, decline towards birth and fall further after the first 2 weeks of postnatal life. The high concentrations of GH throughout gestation are a reflection of the time taken for the neuroendocrine control of GH secretion to develop. In early gestation, GH release from the pituitary is uncontrolled. The decrease in GH after 24 weeks is then associated with the development of the inhibitory mechanisms governing growth hormone release.

Few data exist on the longitudinal changes in GH secretion with age in prepubertal children, but cross-sectional data suggest that GH pulse amplitude increases with age [8]. The most profound changes in GH secretion occur through the pubertal years with a marked increase in the amplitude of GH pulses [8]. Androgens and estrogens both increase GH secretion during puberty.

Maximal levels of GH secretion coincide with the timing of peak height velocity in both sexes and secretion declines thereafter into adulthood. In pre- pubertal and pubertal children, episodic GH

release generates large peaks of GH lasting 1–2 h separated by periods of low basal secretion .Trough concentrations of GH are correlated with body composition and metabolic parameters, while peak concentrations correlate with IGF-I production[9].

Physiological actions of GH and IGF-I on bone growth:

The major role of GH during growth and development is to promote longitudinal bone growth. The somatomedin hypothesis proposes that GH mediates its effects on its target tissues via stimulation of hepatic IGF-I production, which in turn acts as a classical endocrine hormone. In the absence of endocrine IGF-I, autocrine and/or paracrine production of IGF-I is sufficient to sustain normal growth.

The key mediator of GH action in the periphery for both prenatal and postnatal mammalian growth is IGF system. GH exerts its direct effects at the growth plate and indirect effects via IGF1. Better understanding the role of IGF1 on growth had led to the concept of IGF1 deficiency in addition to GH deficiency. With the introduction of recombinant human (rh) IGF1, it is possible to treat conditions due to genetic GH resistance or insensitivity caused by GH

receptor defects and the presence of neutralizing GH antibodies [10].

The growth-suppressing effects of glucocorticoids are also seen in children affected with congenital adrenal hyperplasia(CAH) where high androgens limit the height potential. Most patients with CAH complete their growth prematurely and are ultimately short adults. LinSu,et al., showed that GH in combination with LHRH significantly improved their final adult height in children with CAH [11].

Classification of short stature:

1. Chronic malnutrition
2. Chronic systemic diseases

    Chronic infections like TB

    Chronic renal failure

    Cardiac diseases

    Respiratory diseases

    Collagen vascular diseases

    Inflammatory bowel disease

    Celiac disease

3. Endocrine causes

A. GHD, hypothalamic or a pituitary causes

a. Idiopathic

b. Genetic

i. HESX1

ii. PROP1

iii. POUF1 (Pit1)

c. Mutations within the GH gene

d. Mutation of the GHRH receptor

e. Congenital

i. **Associated with structural defects**

a. Agenesis of corpus callosum

b. Septo-optic dysplasia

c. Holoprosencephaly

d. Arachnoid cyst

ii. Associated with midline facial defects

a. Single central incisor

b. Cleft lip/palate

c. Nasal dimple

f. Acquired

i. Perinatal trauma

ii. Postnatal trauma

iii. Central nervous system infections

iv. Trauma

v. Cranial irradiation

g. Primary tumours of hypothalamus or pituitary

i. Craniopharyngioma

ii. Glioma/astrocytoma

iii. Germinoma

h. Secondary tumours of hypothalamus or pituitary

i. Histiocytosis

ii. Lymphoma

i. Transient

j. Psychosocial deprivation

k. GHD of undefined etiology (idiopathic) (including those with abnormal pituitary morphology on MRI – pituitary hypoplasia, interrupted or hypoplastic stalk, ectopically placed posterior pituitary lobe[12])

B. Larons dwarfism

C. Hypothyroidism

D. Cushing syndrome

4. Familial short stature
5. Constituitional growth delay
6. Chromosomal abnormalities
7. Disorders of bone disease

The true incidence of GH deficiency has not been established with certainty and its prevalence has been reported to be approximately of 1:3500 children.

Clinical presentations:

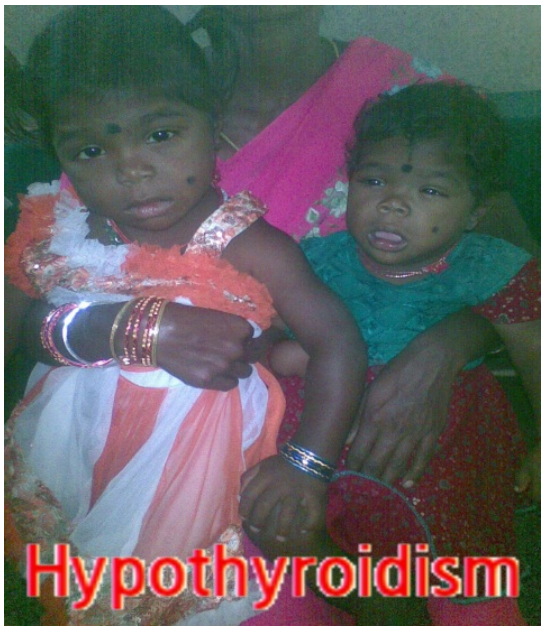
Idiopathic hypopituitarism can present as an isolated hormone deficiency or be part of a combined pituitary hormone deficiency syndrome. In the neonatal period infants usually present with normal birth weight and birth length but impairment of linear growth will occur in the first two years of life. In the neonatal period, episodes of recurrent hypoglycemia, prolonged jaundice or micropenis should alert the physician of the possibility of congenital hypopituitarism. (13,14).

GH deficiency can present as an isolated pituitary deficiency or can be associated with other pituitary hormone deficiencies, the most common being TSH deficiency and less commonly gonadotrophin or ACTH deficiencies. Mineralocorticoid deficiency is rare in children with hypopituitarism since aldosterone secretion is largely independent of pituitary ACTH stimulation.

During early childhood, isolated GH deficiency can present with a classical phenotype of growth failure, protrusion of the frontal bones and poor development of the bridge of the nose. Closure of the


Laron's dwarfism


LARON'S DWARFISM


Hypothyroidism

anterior fontanel may be delayed and dental eruption and skeletal maturation are usually quite delayed. The penis is often small and this may be accentuated by the presence of truncal obesity. Delay of puberty is frequent. However if gonadotrophin function is intact, puberty will develop.

Acquired

Perinatal pathology (prenatal infections, trauma) GH deficiency associated with congenital rubella, toxoplasmosis and cytomegalovirus infections have been described [15]. Perinatal trauma especially associated with forceps delivery, vaginal bleeding and breech presentations [16].

Table 1. Guidelines for initial clinical evaluation of a child with short stature [10]	
Evaluation	**Key elements**
Birth history	Gestational age, birth weight and length, delivery type, birth trauma, hypoglycemia, prolonged jaundice.
Past medical and surgical history	Head trauma, surgery, cranial radiation, CNS infection.
Review of systems	Appetite, eating habits, bowel movements.
Chronic illness	Anemia, Inflammatory Bowel Disease, cardiovascular disease, renal insufficiency, etc.
Family history	Consanguinity, parents and siblings' heights, family history of short stature, delayed puberty
Physical examination	Body proportions (upper/lower segment ratio, arm span), head circumference, microphallus, dysmorphism, and midline craniofacial abnormalities.
Growth pattern	Crossing of percentiles, failure to catch-up.

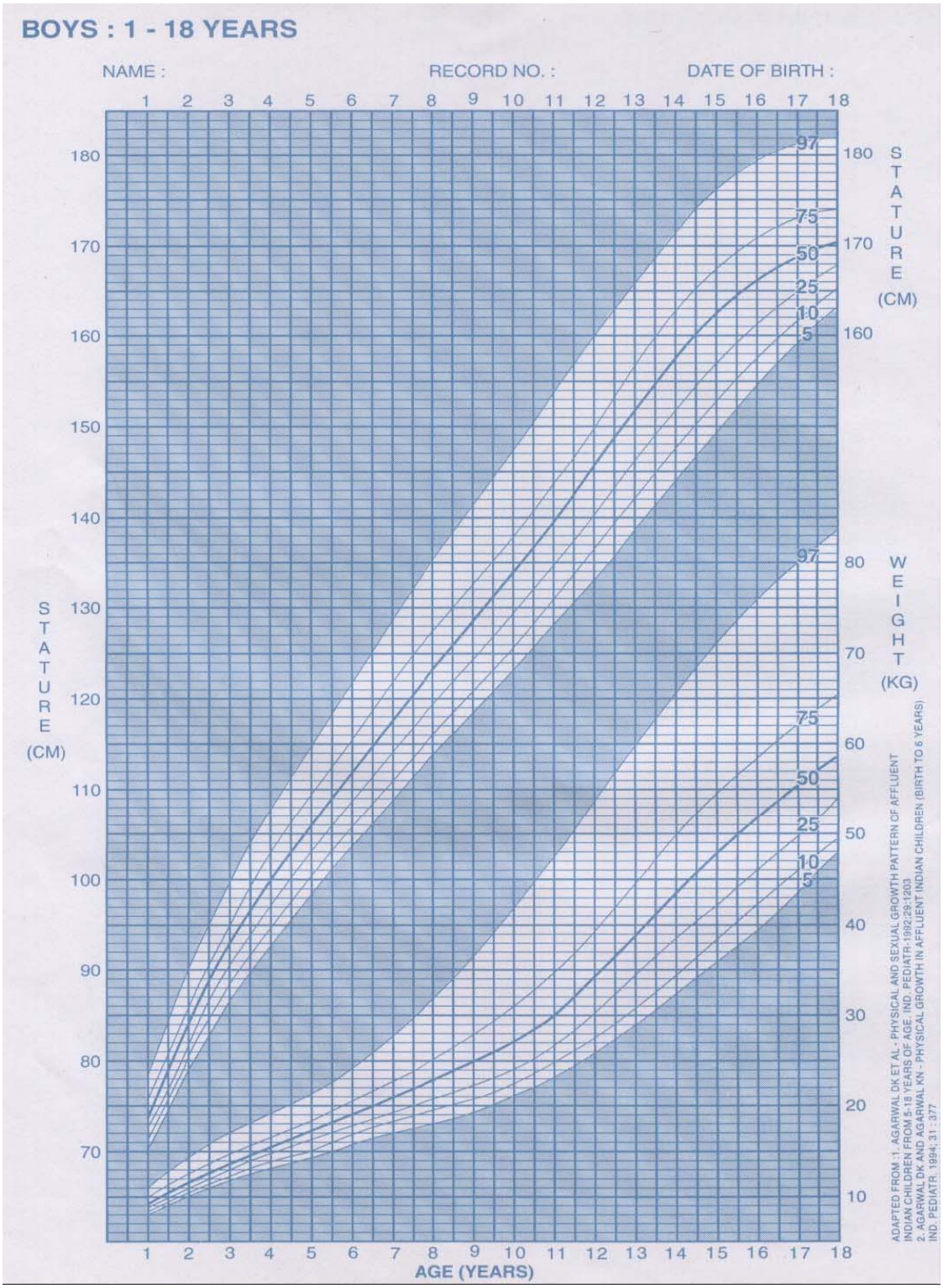
Growth charts:

Commonly used growth charts are the height, weight and BMI charts. Similarly height velocity and proportion charts are essential tools in the diagnosis of short stature. When growth velocity observed over a 6 months or more falls below.

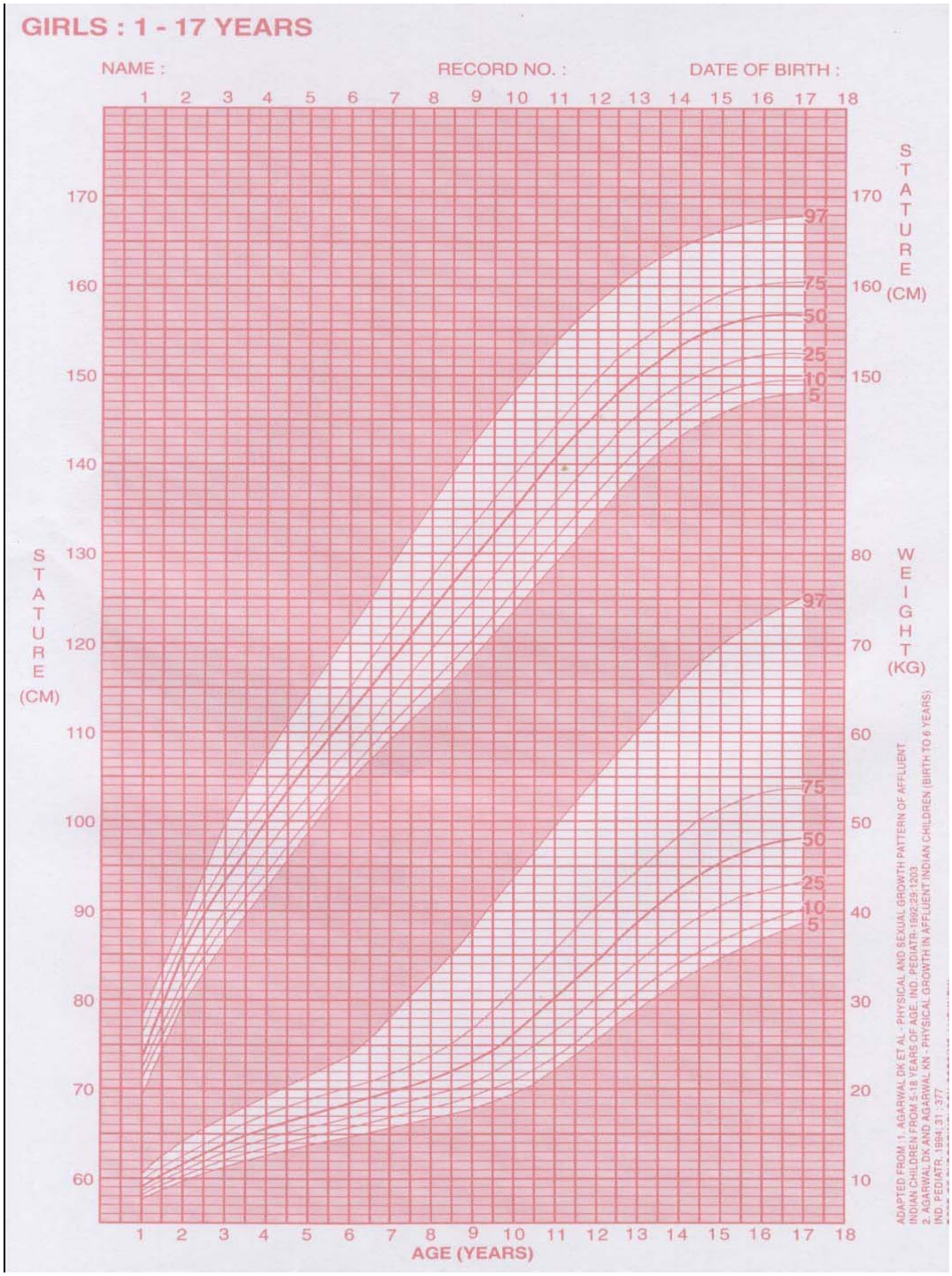
When growth velocity observed over a period of 6 months or more, falls below 25th centile on the velocity chart, is considered abnormal and has more significance than a single height reading below the 3rd centile on a distance chart. Growth velocity is a very sensitive and reliable way to decide whom to investigate.

Height charts are used as a primary screening tool when evaluating a child with short stature. When a child is detected to have short stature, velocity charts are used to follow his or her progress over a period of time.

In 2007, the Indian Academy of Paediatrics published guidelines for growth monitoring incorporating data by Agarwal et al for use by pediatricians in India. In 2006 WHO published a multination study that provides prescriptive growth charts for children under the age of 5 years.[41] WHO recommends use of these growth



AGARWAL GROWTH CHART FIOR BOYS



AGARWAL GROWTH CHART FOR GIRLS

charts for all children under the age of 5 years around the world and government of India has given a directive for use of these charts for under 5 children in India in all areas and across all socio economic classes.[42]

Radiologic evaluation:

The most commonly used system to assess skeletal maturity is to determine the 'bone age' of the left hand and wrist, using the method of Greulich and Pyle [17]. Children younger than 2 years of age should have their bone age estimated from x-rays of the knee. Tanner and Whitehouse and their colleagues developed a scoring system for each of the hand bones as an alternative method to the method of Greulich and Pyle [18].

Adult height prediction methods estimate adult height by evaluating height at presentation relative to normative values for chronological or bone age [19] and are generally considered accurate in evaluating healthy children with a normal growth potential [20,21]. Several different methods have been produced and are currently in widespread use, including those of Bayley-Pinneau, the Tanner-

Whitehouse-Marshall-Carter and Roche-Wainer-Thissen.

Grulich and pyle developed what is commonly known as the predicted adult height (PAH) method of Bayley-Pinneau (BP)[22,23]. The Bayley-Pinneau PAH method is applicable from age 8 years onwards.

Tanner, Whitehouse, Marshall and Carter developed an adult height prediction model based on current height, the mid-parental height, the age of menarche in girls and the Tanner bone age. [18] TW2 differs from the BP method in that the TW2 lowers the minimal age of prediction to 4 years; and also allows for a quantitative effect of bone age, while Bayley-Pinneau give a semi-quantitative effect of bone age (i.e. delayed, normal or advanced).

The RWT predicted adult height method assesses the subjects height, weight, bone age and midparental height (MPH) and then applies regression techniques to determine the mathematical weighting to be applied to the four variables[24].

Biochemical evaluation of GH deficiency:

Several methods have been recommended to assess the adequacy of growth hormone secretion:

1. **Stimulation testing**: GH provocation utilizing arginine, clonidine, glucagon, L-Dopa, insulin, etc. This practice generally measures pituitary reserve or GH secretory ability rather than endogenous secretory status.
2. **GH-dependent biochemical markers- IGF_1 and $IGFBP_3$**: Values below a cut-off less than -2 SD for IGF_1 and/or $IGFBP_3$ strongly suggest an abnormality in the growth hormone axis if other causes of low IGF have been excluded. Age and gender appropriate reference ranges for IGF_1 and $IGFBP_3$ are mandatory.
3. **24-hour or Overnight GH sampling:** Blood sampling at frequent intervals designed to quantify physiologic bursts of GH secretion.
4. **IGF generation test:** This test is used to assess GH action and for the confirmation of suspected GH insensitivity. GH is given for several days (3-5days) with serum IGF_1 and $IGFBP_3$ levels measured at the start and end of the test. A sufficient rise

in IGF_1 and $IGFBP_3$ levels would exclude severe forms of growth hormone insensitivity [100, 25].

Failure to raise the serum GH level to the threshold level in response to provocation suggests the diagnosis of GH deficiency, while a low IGF_1 and/or $IGFBP_3$ level is supportive evidence. Puberty and administration of the sex steroids increase GH response to stimulation tests [27]. To prevent false positive results, some centers use sex steroid priming in prepubertal children prior to GH stimulation testing [28]. In obese children, the normal regulation of the GH/IGF_1 axis is disturbed and GH secretion is decreased. In addition, IGF_1 levels are very sensitive to the nutritional status ($IGFBP_3$ less so), and also that the normative range for IGF_1 and $IGFBP_3$ values are extremely wide, often with poor discrimination between normal and pathological.

Summary of diagnosis of GH deficiency:

Children with severe GH deficiency can usually be diagnosed easily on clinical grounds and fail GH stimulation tests. Studies have shown that despite clinical evidence of GH deficiency, some children

may pass GH stimulation tests [100]. In the case of unexplained short stature, if the child meets most of the following criteria, a trial of GH treatment should be initiated [26].

1. Height >2.25 SD below the mean for age or >2 SD below the midparental height percentile.
2. Growth velocity <25th percentile for bone age.
3. Bone age >2 SD below the mean for age
4. Low serum insulin-like growth factor 1 (IGF1) and/or insulin like growth factor binding protein 3 (IGFBP3)
5. Other clinical features suggestive of GH deficiency.

Key elements that may indicate GH deficiency are:

1. Height more than 2 SD below the mean.
2. Neonatal hypoglycemia, microphallus, prolonged jaundice, or traumatic delivery.
3. Although not required, a peak GH concentration after provocative GH testing of less than 10 ng /ml.
4. Consanguinity and/or a family member with GH deficiency.

5. Midline CNS defects, pituitary hypo or aplasia, pituitary stalk agenesis, empty sella, ectopic posterior pituitary (bright spot) on MRI.
6. Deficiency of other pituitary hormones: TSH, Prolactin, LH/FSH and/or ACTH deficiency.

Many practitioners consider GH stimulation tests to be optional in the case of clinical evidence of GH deficiency, in patients with a history of surgery or irradiation of the hypothalamus/pituitary region and growth failure accompanied by additional pituitary hormone deficiencies. Similarly children born SGA, Turner syndrome, Prader willi syndrome and chronic renal insufficiency do not require GH stimulation testing before initiating GH treatment [(26).]

Treatment:

The principal objective of GH treatment in children with GH deficiency is to improve final adult height.

Administration of rhGH in the evening is designed to mimic physiologic hGH secretion. Treatment is continued until final height or epiphyseal closure (or both) has been recorded.

It is critically important to maximize height with GH therapy before the onset of puberty. Several investigators have advocated modifying puberty or the production of estrogens by the use of GnRH super-analogues [29, 30] and aromatase inhibitors [31-34], respectively, in order to expand the therapeutic window for growth hormone treatment, especially in older males.

REVIEW OF LITERATURE

1. A descriptive observational study was carried out by Choudhri, et al[35] at Kolkata from August 2006 to December 2009 in endocrine out patient department of RGKar Medical College, a tertiary care teaching institution in the eastern part of India involving the children and adolescents referred to the clinic for their growth failure.

The objectives of the this study was to

a) Determine the magnitude of SS among the patients attending a tertiary referral centre
b) Ascertain the pattern of SS, and
c) Find out the etiological profile of SS.

Consecutive patients who attended the clinic with the complaints of growth delay were included in the study. With informed consent, detailed history, clinical examination and laboratory investigations were carried out and information was gathered by administering predesigned and pretested questionnaire. Diagnosed short statured cases were followed up for one year.

Totally 164 short-statured boys and girls were screened out of the 2170 total attendees of the target group. Thus, the proportion of the SS was calculated to be 8%.

	CHOUDHURY, et al
Sample size	164
Place of study	Endo OPD, kolkata
Male to female ratio	1:1.2
Hypothyroidism	29%
GH deficiency	15%
Chromosomal disorders	20%
Normal variants	18%

GH deficiency and hypothyroidism were found to be the commonest cause (26%) of SS among boys. In contrast, chromosomal anomalies were revealed to be the commonest cause (32%) in girls closely followed by hypothyroidism (31%). GHD was the most common cause among boys (26%) compared to chromosomal anomalies (32%) and hypothyroidism (31%) among their counterpart.

2. Another prospective study was conducted by S.K.BHADADA, et al[36] from February 1999 to march 2001 in endocrine clinic at

tertiary referral centre, S.S. Hospital,Institute of medical sciences, BHU, Varanasi.

	Bhadada, et al
Sample size	352
Male : female ratio	1.2 : 1
Common age group	13 to 18 years
Normal variants	36.1%
FSS	15.09%
CGD	21.02%
Birth Asphyxia	8.52%
Endocrine Causes	30.09%

A total of 352 patients of growth retardation have been studied. Of these 194 (55.11%) were males and 158(44.89%) were females. Majority of the patients were seen between the age group of 13 to 18 years. Females outnumbered males in the age group of >18 years. In the remaining age groups male to female ratio was almost equal.

Normal variant short stature (36.1%) [Constitutional growth delay (21.02%) and familial short stature (15.09%)] were the most common causes of short stature followed by endocrine causes (30.09%), IUGR and birth anoxia (8.52%), chronic systemic diseases (7.38%), metabolic bone disease (5.68%) and malnutrition (5.1%). Miscellaneous causes contributed to 6.25%.

The common cause of short stature in male was constitutional growth delay followed by hypothyroidism, miscellaneous causes, systemic diseases, and familial short stature, GH deficiency , mal nutrition and pan hypopituitarism. Familial short stature, Turner syndrome and hypothyroidism were accounted for common causes of short stature in females.

3. In a cross sectional descriptive study which was conducted by sheidey assar, et al [37], the objective was to determine the frequency of GHD in children with short stature. All short stature children referred to endocrinology clinic of Golestan hospital in Ahvaz, Iran during 2005 to 2006 were included if they had height below 3rd percentile for age and sex, no any chronic disorder causing short stature and normal initial investigations. Standard GH stimulation tests were performed and patients with growth hormone maximum level of less than

10ng/dl (in two tests), were considered as growth hormone deficient. Out of 202 cases, 59.9% of them were male and 40.1% of them were female with age range of 1 to 15.

	Sheidey assar, et al
Sample size	202
SS-Male to female ratio	1.49:1
GHD- Male to female ratio	2.4:1
Mean age of SS	9.1 Years
GHD	11.8%

Family history of short stature was positive only in 4.2%. Height standard deviation score (SDS) of 75% of these cases was ≤ -3 and weight for age in 79.2% was ≥ 10 percentile. These data showed significant difference between short and normal children ($P < 0.05$). They concluded the study by saying frequency of GH deficiency was average, compared to other studies. In children with SDS ≤ -3 and weight percentile ≥ 10, GH deficiency should be more considered.

4. Another prospective study was designed by Heshmat moayeri, et al [38] in order to determine the etiologies of short stature with

especial concern on the prevalence of GH deficiency and to compare the results with world-wide studies.

	Heshmat moayeri, et al
Study population	4-18 years
Sample size	426
Mean age	10.8 years
Male female ratio of SS	1.76:1
Male female ratio of GHD	2 : 1
Classic GHD	23.4%

In total 426 subjects, boys were 272 and girls were 154 among 4-18 years with short stature. The decision to investigate the growth hormone axis was taken with the knowledge that other explanations for growth failure have been excluded by documention of a normal full blood count, ESR, renal function and measurement of serum thyroxine concentration. In some female subjects, a karyotype was performed to exclude Turner's syndrome. Bone age was studied in all subjects.

They found that normal variants of growth including constitutional growth delay and familial short stature were identified as the most common causes of growth failure in this study. The results obtained in this study were in agreement with world-wide reports.

Boys outnumbered girls by 2:1 ($p < 0.05$).They concluded that most children with short stature will not have an endocrine disorder, but in endocrine referral centers, the frequency of GH deficiency is higher than in general clinics and (2) GH deficiency appears to be more common in boys.

5. A prospective study on profile of growth hormone deficiency[40] was done in Pediatric Endocrine Division, Bai Jerbai Wadia Hospital for Children, Institute of Child Health and Research Centre, mumbai by meena desai, et al. Of the 430 children referred for the evaluation of SS, 100 (23%) were confirmed to have growth hormone deficiency. The male to female ratio was 1.94 : 1. Less than 10% belonged to the lower socio-economic group. Most of the cases (73%) presented between the ages of 6-15 years though growth failure was usually recognized earlier.

	Meena desai et al
Sample size	430
GHD	23%
Common Age Group for SS	6-15 years
Larons dwarfism	11%
Abnormal presentation	24%
Birth asphyxia	24%
MPHD	12%
Mean Peak level of GH in GHD	1.52 ± 1.36
Mean Peak level of GH in Larons	62.8 ± 19.8

Seventy five GH deficient children had idiopathic GH deficiency and 31% of these were familial .Fourteen had organic causes and 11 had GH resistance. 0f the 75 with IGHD, 18 had abnormal deliveries, breech or birth asphyxia. Multitropic pituitary hormone deficiency was found in 9/75 cases of idiopathic GH deficiency and in three of the organic group. The height age was much

more retarded than chronological age in the GH resistant group ($p \sim 0.05$) and the HA/BA ratio was also lowest in this group ($p \sim 0.001$).

The interesting feature of this study is the marked predominance of the familial cases (31%) and a high incidence of growth hormone resistant cases (11%). The mean peak levels of GH in normal controls were very significantly higher (20.1 + 1.36 ng/ml) than the mean peak levels of children with GH deficiency (1.52 + 1.36 ng/ml). Very high peak levels (62.8 + 19.8 ng/ml) were obtained in the GH resistance group.

In the GHR group the basal GH levels were noted to be high in 6 of the 11 children ranging between 6 to 41 ng/ml (normal , 5 ng/ml) with a mean level of 26.2 ± 14 ng/ ml while as in the remaining five, the basal levels ranged between 1.28 to 4.93 ng/ ml, with a mean level of 3.47 ± 1.34 ng/ml. The levodopa + propranolol test (used as a second test in 24 GH deficiency children) showed a stimulated mean peak level of 1.1 ± 1.07 ng/ml and the mean peak level with insulin testing was 2.24 + 2.1 ng/ml in those children with GH deficiency where it was done as one of the two tests. A second test for GH was not necessary and was not done in the GH resistance group.

Colaco, et al[54] found 57% of endocrine causes .Among this , 52% were due to GH deficiency. According to colaco, et al, a study

conducted in Bombay showed nutritional disorders and chronic systemic infections were the most common cause. Among endocrine causes, GH deficiency were seen in 97 (68%) and hypothyroidism in 27 cases (18%) out of 143 cases.

Suraj gupte[55] found out that 10% of cases were due to endocrine cause of 300 consecutive children. Vimbani[56] et al found severe GH deficiency in 1 per every 4000 children from a study of 48000 scottish school children.

AIM OF THE STUDY

To study the following parameters in short stature children attending endocrine OPD, ICH.

a) Magnitude of SS among the patients attending a tertiary referral centre.
b) Ascertain the pattern of SS
c) Find out the etiological and clinical profile of SS.
d) Anthropometric measurements
e) Dynamic GH study using clonidine stimulation test

To find out the possible risk factors for short stature growth hormone deficiency.

STUDY JUSTIFICATIONS

Short stature is a common pediatric endocrine problem. Since normal growth is a barometer of health in childhood, any child who is growing normally, virtually excludes chronic physical or mental illnesses. Hence, yearly evaluation of height and weight of all children is mandatory to assess their growth potential. The short stature, although not a disease per se, is a manifestation of several diseases. Its early diagnosis and treatment is most of the time rewarding.

Western literature is replete with studies on short stature; there are very few studies from Indian subcontinent. Since multiple factors viz. genetic, prenatal, postnatal and local environmental factors, affect the growth, their relative significance would be variable in different populations.

To study these etiological factors, present study has been designed.

MATERIALS AND METHODS

Methodology:

Study design – Descriptive study

Study period – Nov 2009 to oct 2011

Study place – paediatric endocrine OPD,ICH

Study population:

Inclusion criteria

1. Height <5TH percentile of Agarwal growth charts
2. Growth rate below the fifth percentile for chronological age for local population (Agarwal's growth chart)
3. Children referred to endocrine OPD as short stature .

Exclusion criteria

1. Those with height >5th percentile
2. Any lab investigation showing rickets, liver disease, nutritional disease, chronic systemic infections & inflammation.
3. Hypotensives.

Sample size - All children with the above inclusion criteria who presented during the study period (84 cases).

Ethical committee clearance was obtained from the Institutional review board.

Maneuvre:

Cases were recruited based on inclusion and exclusion criteria after obtaining informed parental consent.

Subjects with Ht <5th centile after excluding all systemic causes

↓

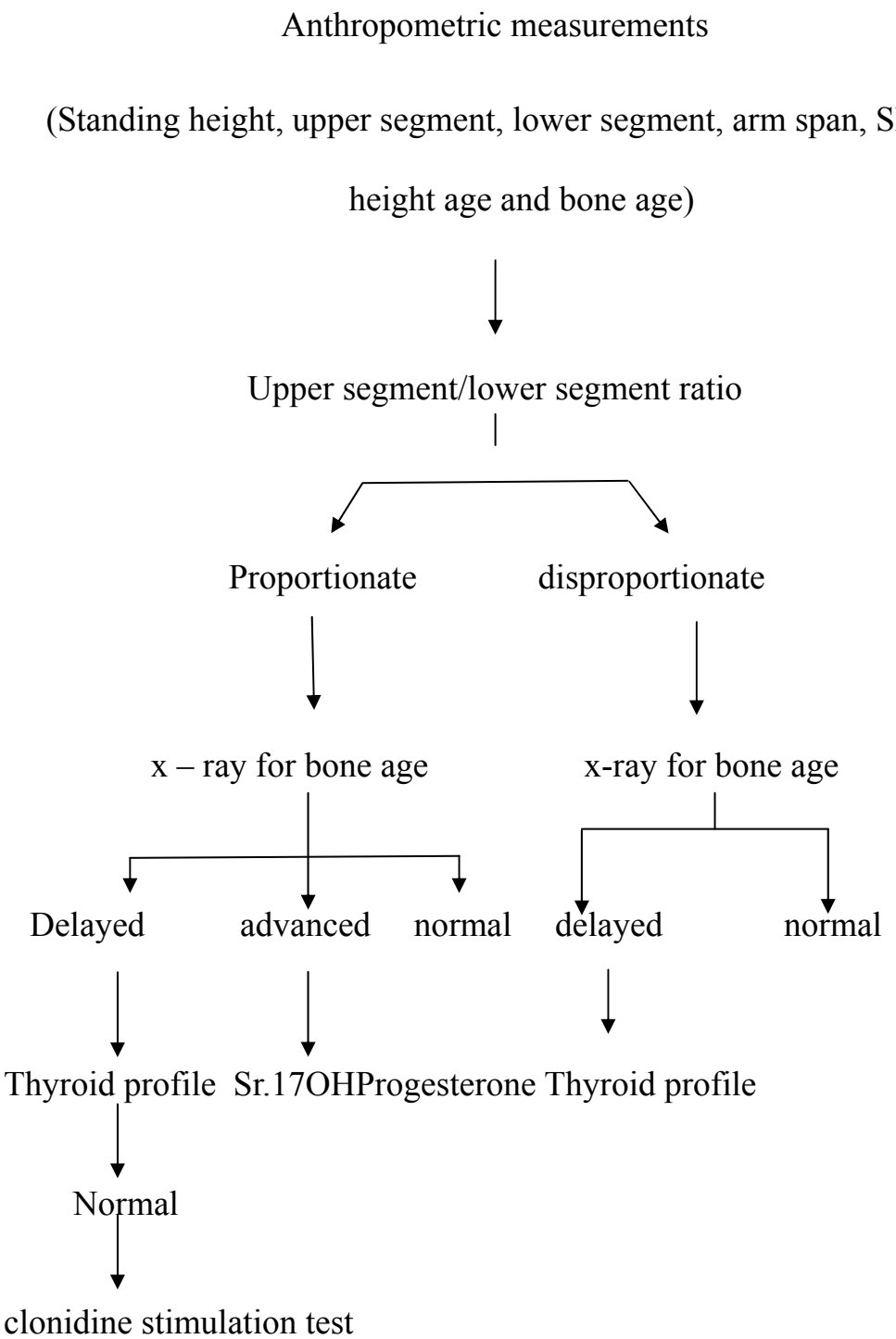
Detailed history taking, thorough physical examination and investigations.

↓

(Symptoms to r/o systemic diseases, nutritional disorders, chronic infections, H/O consanguinity, family H/O short stature , APH mode of delivery, presenting part ,neonatal hyperbilirubinemia,

↓

development, hypoglycemic attacks, dysmorphic facies, constipation , history suggestive of increased ICP, genitalia examination & fundus examination)



Standing height:

It was measured on a height scale with heels, buttocks, shoulders and occiput against a vertical board and the head is positioned in Frankfurt plane (outer canthi of eyes at horizontal plane with upper border of tragus. The children were drawn upto their full height by upward pressure on the mastoids).

Arm Span:

It was measured with the child standing, arms fully extended parallel to the floor and palms facing forward. With parent's assistance, the distance between middle finger was measured using tape.

Upper Segment, Lower Segment:

The upper segment extends from vertex to pubis, lower segment extends from pubis to heel. First lower segment was measured and upper segment derived by substracting LS from standing height.

Height Age:

Height age means the age which corresponds to the Ht. in cm along 50^{th} centile curve.

Bone Age:

Bone age assessment was done on skiagram of pelvis, knees, left hand wrist, and left elbow following a standard chart based on a study at Radiology department of Institute Of Child Health and Hospital for Children, Chennai.

Growth Formula:

Height age < bone age < chronological age – Familial SS

Bone age = height age < chronological age – CGD

Bone age < height age < chronological age – GH Deficiency

Target height:

Growth is strongly related to the genetic potential. A child's midparental height is calculated as follows:

- Girl = (height of mother in inches + height of father in inches)/2 - 2.5 inches
- Boy = (height of mother in inches + height of father in inches)/2 + 2.5inches.

This value plotted as adult height at 18 years and the spread for target range is 6 cm on either side of the target height. This then becomes target range and if the child's height is within these percentiles, it is considered as normal. A short child who is growing close to his/her target height percentile is likely to have familial short stature. [15] . The child's present height was projected along the percentile curve to get the anticipated adult height and correlated with mid parental height. Growth deceleration during the first 2 years followed by a normal growth velocity, with acceleration late in adolescence, leading to a final height that is close to the target height suggests constitutional delay in growth and development.

Auxological data mainly target height, child's current height , height velocity and body proportions are some of the important tools for proper evaluation and management of SS. Judicious use of these techniques will reduce the cost of subsequent investigations.

Clonidine stimulation test:

In the morning after overnight fasting, 5 ml of venous sample was drawn for basal level of GH estimations. Then the child was given oral clonidine

4 microgram/kg body weight. Blood samples were drawn at 30 mins, 60 mins, and 90 mins in three separate non-heparinised tubes. During the procedure, the subjects were kept in recumbent position and blood pressure were recorded half hourly but no fall in BP were noted.

Hormone assay :

Sera separated aliquated and stored at -20º C in a deep freezer until assayed. GH estimation was done at pediatric APOLLO Hospital using Radio-immunoassay (RIA) kit supplied by BARC. The tests cover a range of 0-40 ng of GH per ml of serum with an intra-assay and inter assay variability ranging between 5-10%. Only basal and post clonidine values were taken into account. Peak value >7 ng/ml is normal. Value <7 ng/ml-partial GHD and <3.5 ng/ml-complete GH deficiency.

TSH assay was done in all subjects using the TSH Immuno Radiometric Assay (IRMA) kit supplied by BARC ,Bombay. The sensitivity is 0.07 microunits/ml. The TSH values taken as normal in ICH ,Egmore is 0.2-4 microunits /ml.

IGF_1 : IGF_1 estimation was done to rule out pure GH deficiency, Larons dwarfism.

MRI Brain : MRI Brain was done to rule out CNS pathology.

STATISTICAL ANALYSIS:

The parameters are evaluated using CHI SQUARE test and SPSS16 Version. P value < 0.05 is considered significant.

OBSERVATION

Totally 84 children with short stature were studied in the age group less than 12 years.

Demographic characteristics of children with short stature.

Total no. of males = 33(39.3%)

Total no. of females = 51(60.7%)

Female predilection was observed. The study population comprises 33 (39.3%) males and 51 (60.7%) females, there is no significant difference (p = 0.052) in male female distribution among the study population.

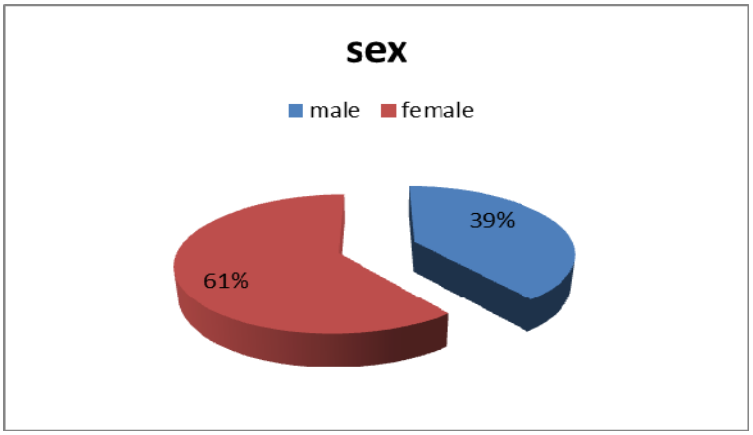


Fig. 1Sex Distribution Among Children With Short Stature

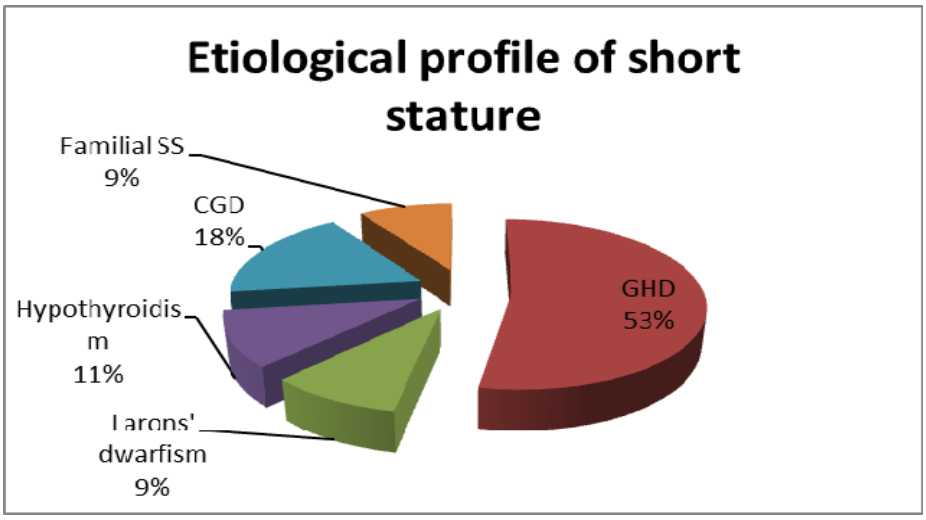


Fig.2 Etiological profile of short stature

Out of study population of 84 cases, most commonly observed etiology among endocrine causes was GH deficiency (53%) followed by constitutional growth delay (18%), hypothyroidism (11%), larons dwarfism (9%) & familial short stature (9%) .

TABLE 1. AGE & SEX DISTRIBUTION IN STUDY POPULATION

AGE GROUP	MALE n =33	FEMALE n =51	TOTAL n = 84
2-5 YEARS	11(44%)	14(56%)	25 (29.8%)
6-9 YEARS	12(37.5%)	20(62.5%)	32 (38.1%)
10-12 YEARS	10(58.8%)	17(41.2%)	**27 (32.1%)**

Of the total study population, clustering (38.1%) of short stature noted in 6 to 9 years age group. Comparatively lesser number of cases were affected with SS in 2 to 5 years (29.8%).

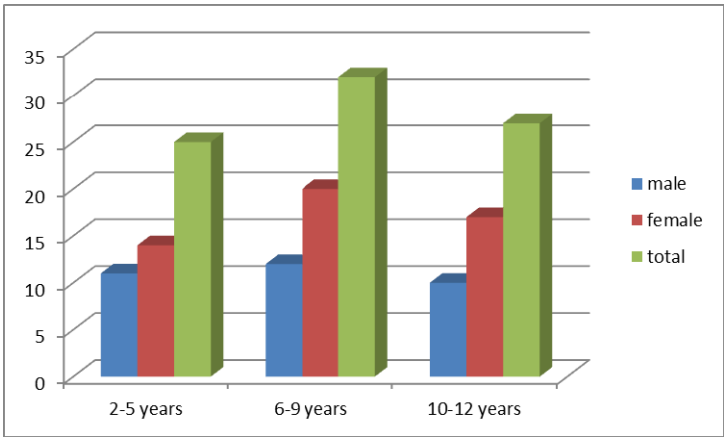


Fig. 3 AGE AND SEX DISTRIBUTION OF SHORT STATURE

TABLE 2. GHD distributioon among various age group

Age group	GHD	Non GHD	TOTAL	P Value
2-5 years	14 (26.4%)	11 (35.5%)	25 (29.8%)	0.413
6-9 years	23 (43.4%)	9 (29%)	32 (38.1%)	
10-12 years	16 (30.2)	11 (35.5%)	27 (32.1%)	

Maximum number of short stature were observed in 6 to 9 years group followed by 10 to 12 years group. Whereas maximum cases of GH deficiency is seen in 6 to 9 years (43.4%)group followed by 10 to 12 years group with 30.2% and finally 2 to 5 years group with 26.4%. The observed difference is statistically not significant (p=0.413).

Out of 53 children with GH deficiency, 14 (26.4%) were less than 5 year of age, 23(43.2%) belong to the age group 6 to 9 years ,16 (18.2 %) belong to the age group 10 to 12 years. Out of 21 children with non GH deficiency causes, 11 (35.5%) were less than 5 year of age , 9(29%) belong to the age group 6 to 9 years ,11 (35.5 %) belong to the age group 10 to 12 years. There is no significant difference in the distribution between these groups.

TABLE 3.AGE Vs SEX

Chronological age	**n**	**Minimum .age**	**Maximum .age**	**Mean ± SD**
TOTAL	84	2	12	7.25 ± 3.33
Male	33			7.24 ± 3.26
Female	51			7.25 ± 3.41

In this study of short stature, we had seen wide variations in age distribution ranging from 2 years to 12 years. Of total cases of short stature, mean age of presentation was 7.25 ± 3.33. It was almost similar in both sexes i.e.male-7.24 ± 3.26 and in female SS children 7.25 ± 3.41.

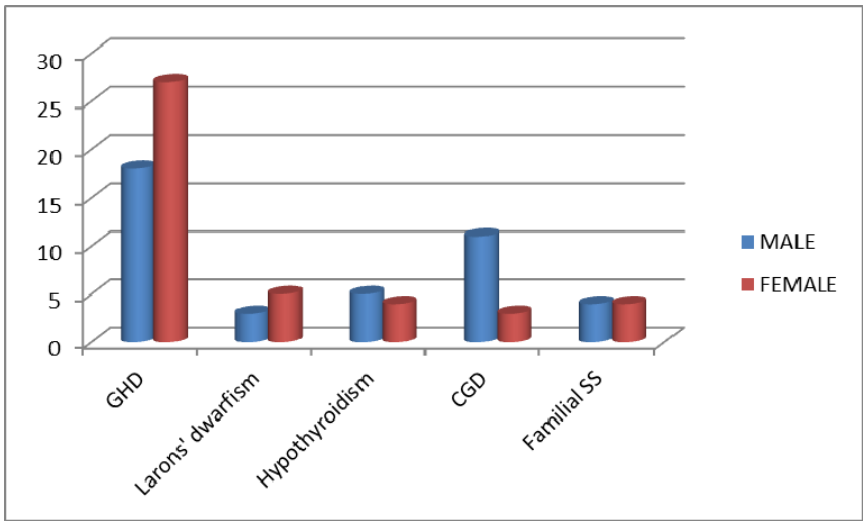


Fig 4.SEX Vs Various diagnosis

In GH deficiency, females were dominantly affected than males. Similar finding was observed in Larons dwarfism. Males were predominantly affected with hypothyroidism, constitutional growth delay. Both male and female were equally affected in familial short stature..

Table 4. Perinatal features & clinical symptom among children presented with short stature

SYMPTOMS	N	Percentage
Increased ICP	1	1.9%
APH	5	9.4%
Maternal Fever	9	16.9%
Normal delivery	42	79.2%
Pre Term	15	28.3%
Birth asphyxia	33	39.3%
Breech	58	69%
NNH	15	17.9%
Neonatal hypoglycaemia	12	14.2%
Consanguinity	49	58.3%
Family history	8	9.5%
Parental history of delayed puberty	14	16.7%
Microphallus	8	9.5%
Hyper pigmented skin	10	11.9%
Dysmorphic facies	41	48.8%
Hypothyroidism	12	14.2%
MPHD	10	11.9%

The study population was analysed based on their clinical symptoms and presentation. We observed raised ICP in 1(1.9%), antepartum hemorrhage in 9.4%), maternal fever in 9 (16.9%)cases, normal delivery in 42 (79.2%), preterm delivery in 15 (28.3%), birth asphyxia in 33 (39.3%), breech presentation in 58 (69%), NNH in 15 (17.9%), neonatal hypoglycemia in 12 (14.2%), consanguinity in 49 (58.3%), family history in 8 (9.5%),parental history of delayed puberty in 14 (16.7%), microphallus in 8 (9.5%), hyperpigmented skin in 10 (11.9%), dysmorphic facies in 41 (48.8%), hypothyroidism in 12 (14.2%) and MPHD in 10 cases(11.9%).

TABLE 5.Comparison of breech delivery among GHD & non GHD group of children with short stature

BREECH	GHD (n = 53)	Non GHD(n = 31)	P Value
Present	**28 (52.8%)**	**6(19.4%)**	**0.005**
Absent	**25(47.2%)**	**25(80.6%)**	

28 cases were born with breech presentation of total 53 cases of GH deficiency. Whereas only 6 children born with breech presentation in non GH deficiency. .P value is 0.005 which is significant.

TABLE 6.Distribution of birth asphyxia in GHD vs. non GHD

Birth asphyxia	GHD (n = 53)	Non GHD (n=31)	P Value
Present	**26 (49.1%)**	**7 (22.6%)**	**0.017**
Absent	**27 (50.9%)**	**24(77.4%)**	

Totally 26 cases suffered from birth asphyxia during delivery. P value is 0.017 which is significant.

TABLE 7. Distribution of NNH in GHD

Neonatal hyper-bilirubinemia	GHD (n=53)	Non GHD (n=31)	P Value
Present	**13(24.5%)**	**2(6.9%)**	**0.037**
Absent	**40(75.5%)**	**29(93.1%)**	

Totally 13 cases suffered from NNH during neonatal period. P value is 0.037 which is significant**.**

TABLE 8. Distribution of Birth Weight in Short Stature

Birth weight	Number	Percentage
Below 1 kg	**2**	**2.38%**
1-1.5 kg	**6**	**7.14%**
1.5-2 kg	**8**	**9.52%**
2-2.5 kg	**19**	**22.61%**
Above 2.5 kg	**49**	**58.33%**
Total	**84**	**100%**

Totally 49 cases out of 84 cases had relatively normal birth weight (BW>2.5kg) which contributes about 58.33%. Rest of them had low birth weight that comes around 41.67%.

TABLE 9.Distribution of Consanguinity in GHD

Consanguinity	GHD (n=53)	Non GHD (n=31)	P Value
Present	**31(58.4%)**	**18(58.1%)**	**0.970**
Absent	**22(41.6%)**	**13(41.9)**	

Totally 31 cases were born out of consanguineous marriage out of 53 cases of GHD. P value is 0.970 which is insignificant.

TABLE 10. Distribution of dysmorphic facies in GHD

Dysmorphic facies	GHD (n=53)	Non GHD (n=31)	P Value
Present	**41(77.3%)**	**0(0%)**	**0.0**
Absent	**12(22.7%)**	**31(100%)**	

Totally 41 cases were born with dysmorphic facies (like midfacial crowding, central incisors, cleft lip & palate) out of 53 cases of GHD. P value is 0.0 which is significant.

TABLE 11. Clonidine stimulation test (CST) in short stature

CST		n	Mean ± SD
GH – Basal	**GHD**	**45**	**1.45 ± 1.54**
	Larons dwarfism	**8**	**26.22 ± 13.98**
	Non GHD	**5**	**5.41 ± 4.29**
GH – Postclonidine	**GHD**	**45**	**1.99 ± 1.78**
	Larons dwarfism	**8**	**48.64 ± 11.63**
	Non GHD	**5**	**12.73 ± 11.78**

Observed mean value of basal GH level – 1.45 ± 1.54 in GHD, 26.22 ± 13.98 in Larons,5.41 ± 4.29 in non GHD and mean postclonidine GH level – 1.99 ± 1.78 in GHD, 48.64 ± 11.63 in Larons, 12.73 ± 11.78 in non GHD.

TABLE 12. Clonidine stimulation test in true GHD & Larons dwarfism

		GH basal	30 min	60 min	90 min
GHD(n=45)	Mean ± SD	1.45 ± 1.55	1.56 ± 1.76	2.19 ± 2.19	2.2 ± 2.61
Larons dwarfism(n=8)	Mean ± SD	26.21 ± 13.98	47.62 ± 23.52	49.99 ± 15.44	48.29 ± 16.45

TABLE 13. Various Auxological parameters in short stature

	CA	HA	HA lag	BA	BA lag	HA/BA	HA/CA
GHD	7.37 ±	3.06 ±	4.3 ±	3.96 ±	3.38 ±	0.95 ±	0.39 ±

(n=45)	**3.35**	**2.09**	**2.36**	**2.63**	**2.02**	**0.89**	**0.18**
Larons Dwarfism (n=8)	**6.25 ± 2.87**	**1.96 ± 1.92**	**4.29 ± 2.41**	**2.69 ± 1.49**	**3.69 ± 2.22**	**0.63 ± 0.34**	**0.3 ± 0.22**
Non GHD(31)	**7.34 ± 3.47**	**3.7 ± 2.52**	**3.66 ± 1.59**	**5.16 ± 3.16**	**2.24 ± 1.66**	**0.72 ± 0.42**	**0.45 ± 0.19**
TOTAL (n=84)	**7.25 ± 3.33**	**3.19 ± 2.27**	**4.06 ± 2.17**	**4.29 ± 2.84**	**2.99 ± 1.97**	**0.83 ± 0.71**	**0.4 ± 0.19**

HA / BA is useful in knowing the relative severity of retardation of one component over the other. The correlative study between HA / BA was analysed in the present study consisting of 3 groups GH deficiency, Larons dwarfism and non GHD and found to be 0.95,0.63 and 0.72 respectively. We can make out that both mean height age and mean bone age retarded in larons dwarfism than GHD. In both GHD and larons dwarfism, mean height age is more retarded than mean bone age.

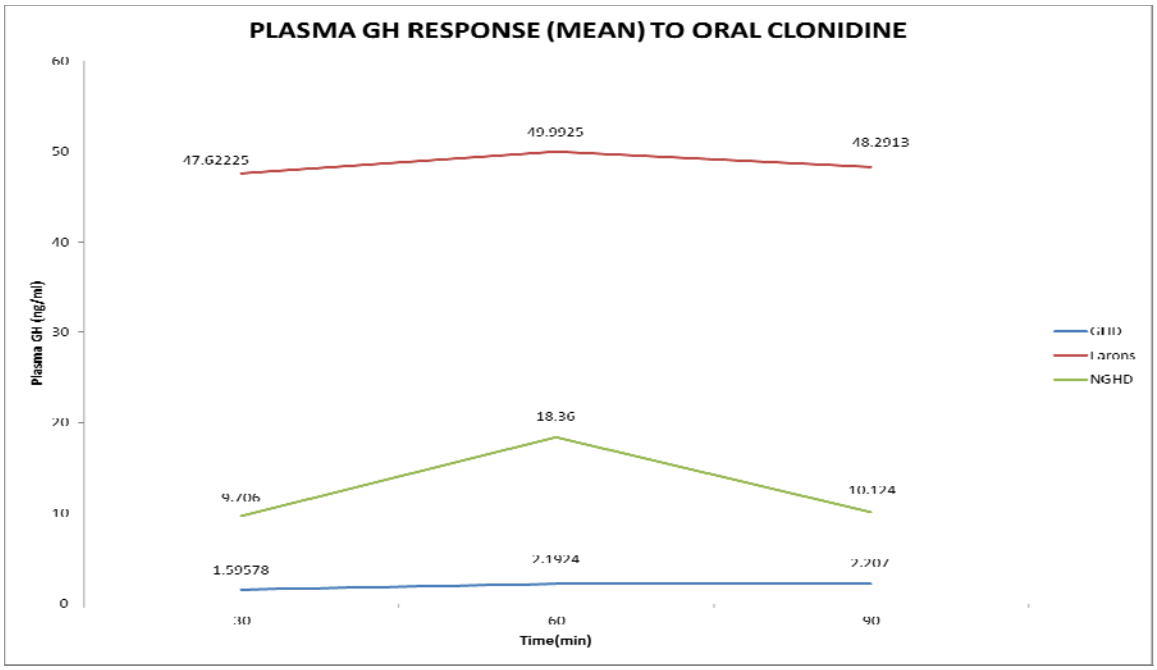


Fig. 5

This is graphical representation of mean level of GH secretion in response to oral clonidine at various intervals.

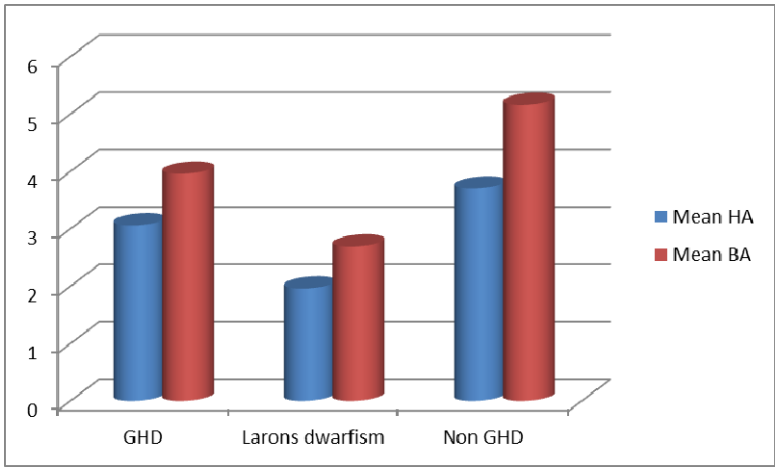
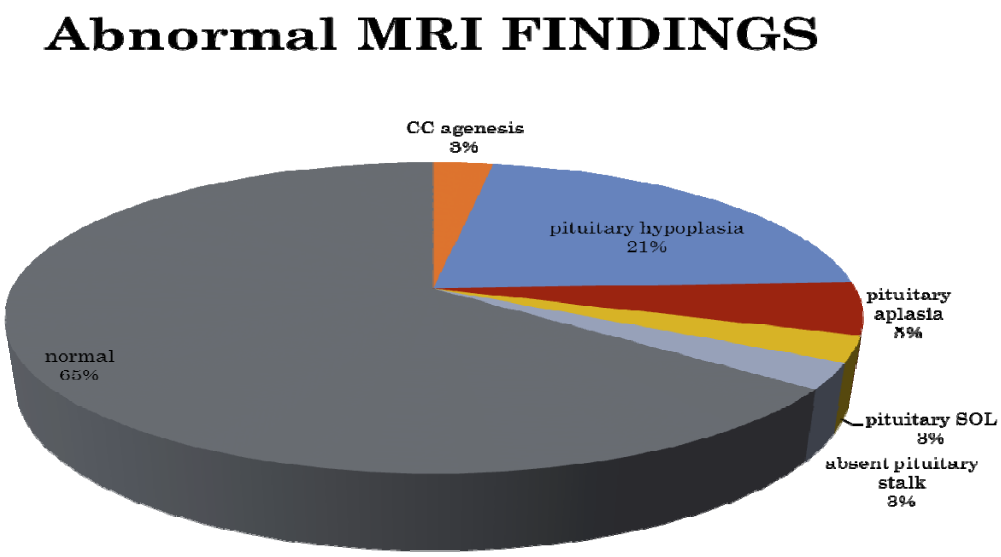


Fig. 6

In this figure, we can make out that both mean HA and mean BA retarded in larons dwarfism than GHD. In both GHD and larons dwarfism, mean HA is more retarded than mean BA.



Of total study population, 21% of children had pituitary hypoplasia, 5% had pituitary aplasia, 3% had pituitary SOL, 3% had absent pituitary stalk whereas remaining 65% had normal MRI Brain study.

DISCUSSION

This descriptive study was conducted at Institute of Child Health to find out the demographic characteristics , clinical and etiological profile of short stature in children between 2 to 12 years of age attending endocrine OPD. 84 children between 2 to 12 years of age getting admitted at Institute of child health who met the inclusion and exclusion criteria were recruited.

We had

1. 45 cases of (53.6%) true GH deficiency
2. 8 cases of (9.5 %) Larons dwarfism
3. 9 cases of (10.7 %) hypothyroidism
4. 8 cases of (9.5%) familial short stature
5. 14 cases of (16.6%) constitutional short stature.

Short stature may be a disability and can be a distress to the victimised child or adolescent[43]. So, short stature should be assessed early before the epiphysial fusion to get the opportunity of medical management. Extent of short stature as revealed in this study is higher than what was reported by Colaco et al.[44] i.e. a prevalence of 5.6% in

2500 children admitted in hospitals. Khadgawat et al[45] have reported 7% prevalence among 280 normal school children. Another observation made by Colaco revealed a prevalence of 10% short stature in children utilizing outpatient services. However, Garg [46] in his study of short stature in Indian Children had reported 13.8% prevalence of short stature, lesser than that of our study. In this study, the prevalence of short stature was 15.6%.

Bhadada et al reported normal variants as the predominant cause. Also they observed pituitary disorders in 19.2%, Celiac disease in 13.7% and Primary hypothyroidism among 13.7% cases of SS in 2005-2007 compared to their findings of primary hypothyroidism in 18.4%, pituitary disorders in 15.21% and nutritional disorders in 17.4% cases of short stature in 1995-1996. This prevalence of pituitary disorders is comparable to our study which was 20.2%. Whereas prevalence of hypothyroidism is 11% which is lesser than that of Bhadada et al study (18.4%). This variation in etiological profile could be due to difference in study population, cultural practices and health care facilities. The changing trend is reported to be due to high index of suspicion and wider availability of screening tests.[47]

	CHOUDHURY, et al	In our study
Sample size	164	84
Place of study	Endo OPD, Kolkata	Endo OPD, Chennai
Male to female ratio	1:1.2	1:1.54
Hypothyroidism	29%	10.7%
GHD	15%	63.1%
Normal variants	18%	26.1%

Eventhough both studies were conducted at endocrinology OPD, there is wide variation in etiology.In our study, the most common cause is GH deficiency followed by normal variants of growth delay and hypothyroidism. Whereas Choudhury, et al study showed hypothyroidism as primary cause of short stature followed by normal variants of growth delay and GH deficiency.[35]

This variation in etiological profile could be due to difference in study population, cultural practices and health care facilities .The changing trend is reported to be due to high index of suspicion and wider availability of screening tests.

	Bhadada, et al	In our study
Sample size	352	84
Male : female ratio	1.2 : 1	1:1.54
Common age group	13 to 18 years	6 to 9 years
Normal variants	36.1%	26.1%
FSS	15.09%	9.5%
CGD	21.02%	16.6%
Birth Asphyxia	8.52%	39.3%
Endocrine Causes	30.09%	73%

There is female preponderance observed in our study in contrast to Bhadada et al study where slight male predominance[36] is seen. Common age group cannot be compared since their study populations were upto 18 years. Our study population is between 2 to 12 years. Bhadada et al study showed normal variants of growth delay as most common cause followed by endocrine causes. Etiological profile could not be compared because sample size is large in their study. Both studies were done at different periods of time in different population.

	Sheidey assar[37], et al	In our study
Sample size	202	84
SS-Male to female ratio	1.49:1	1:1.54
GHD- Male to female ratio	2.4:1	1:1.52
Mean age of SS	9.1 Years	7.25 years
GHD	11.8%	63.1%

In a study done by shiedey assar et al, GH deficiency incidence was 11.8% which was more commonly seen in males as general short stature incidence. Here GH deficiency incidence is much lower than our study. In contrast to their study, females were more commonly affected than males in our populations.

	Heshmat moayeri[38], et al	In our study
Study population	4-18 years	2-12 years
Sample size	426	84
Mean age	10.8 years	7.25 years
Male female ratio	1.76:1	1:1.54
Classic GHD	23.4%	53.6%

Heshmat et al found that males outnumbered females in classic GH deficiency whereas in our study females were predominantly affected. They conducted study in large population of short stature . And our sample size was only 84. So further studies need to be conducted in larger population in our country.

	Meena desai[40], et al	In our study
Sample size	430	84
GHD	23%	63.1%
Common Age Group for SS	6-15 years	6 To 9 years
Larons dwarfism	11%	9.5%
Abnormal presentation	24%	52.8%
Birth asphyxia	24%	49.08%
MPHD	12%	18.8%
Mean Peak level of GH in GHD	1.52 ± 1.36	1.99 ± 1.78
Mean Peak level of GH in Larons	62.8 ± 19.8	48.64 ± 11.63

In general, we had higher number of cases as GH deficiency which was the most common endocrine cause in our study because the study was done at ICH which is a tertiary referral centre and most of

the normal variants of growth disorders would have been screened at peripheral hospital itself. Only those with pathological short stature would have been referred to higher centres. Hence we had higher incidence of GH deficiency rather than normal variants of growth delay.

Perinatal insults like birth asphyxia were found in 33 cases(62.3%) of GH deficiency in the present study similar to the Western studies [48,49] which observed 50-60% incidence.

Familial clustering was observed in 9.5% in the present study, less than that observed in Bombay based study (31%)[50] but more than that was observed by western investigators (3-5%)[48,51].

High incidence of consanguineous parentage (58.3%) was observed in the present study. This is much higher than any other previous Indian studies. One interesting finding observed was that consanguineous parentage was found in all the cases due to GH insensitivity syndromes. William et al[52] also found similar incidence.

Even though the typical features of GH deficiency was found in 48.8% of cases , the truncal obesity was found only in one case. This may be due to the associated nutritional and environmental insults in our country.

Unlike previous Indian studies, the maximum number of short children presented in the 6 to 9 years age group (64.3%). This is due to lack of awareness and lack of insight which postponed the desire to seek medical advice.

There were 10 cases who had history suggestive of hypoglycemic attacks. Herber et al[52] identified 11 children with hypoglycemic attacks out of 29 GH deficiency children, all of them were less than 2 years old.

All the male children in the present study were noticed to have microphallus similar to previous studies.

According to Kaplan et al[53] , the degree of delay in bone age in GH deficiency is usually equivalent to delay in height age. But in the present study the retardation of height age was more severe than that of bone age.

Colaco et al[50] in his study of 100 cases of GH abnormalities, found height age was more severely retarded than bone age in Larons dwarfism unlike GH deficiency. In the present study, it was observed more severe retardation of HA in both GHD and Larons dwarfism.

LIMITATIONS

- The sample size is small.
- The study was done at a tertiary care centre ,So the study population does not reflect the general population.

SUMMARY

The assessment of linear growth is one of the most sensitive means of evaluating all overall wellbeing of a child because ir gives a net expression of genetic make up, adequacy of nutrition, environment and residual effect of previous disease. Expression of stature in childhood is reinforced by GH,Thyroxine, sex steroids,cortisol and various growth factors.

Recent development in pediatric endocrinology has thrown light on the actions of growth hormone and growth factors. Understanding its significance will pave way for proper approach to short stature children.

A descriptive study on Epidemiology, Clinical profile , Etiology of short stature children aged 2 to 12 years was conducted in the department of pediatric endocrinology. 84 children diagnosed to have pathological short stature met the inclusion and exclusion criteria and they were recruited for the study after obtaining informed consent. Details regarding clinical history and relevant investigations were entered in prestructured proforma. The proportion of various outcome measures were arrived and statistical analysis done using Chi Square test . P value < 0.05 was considered significant.

CONCLUSION

In children who attended endocrine OPD with pathological short stature were analysed for etiological and clinical profile. This study shows true growth hormone deficiency as the most common cause followed by normal variants of growth delay and hypothyroidism. 10(18.6%) out of 53 cases of GH deficiency had MPHD.

Of GH deficiency children, statistically significant proportion of children had association with breech presentation, birth asphyxia, neonatal hypoglycemia and hyperbilirubinemia. Significant number of persons had hypoplastic or absent pituitary in MRI Brain. Severity of growth delay is more evident with larons dwarfism than GH deficiency while considering its low HA/BA ratio. MRI Brain plays vital role in making etiological diagnosis of short stature.

We conclude that the findings can frame our mindset to remain vigilant about the problem for detection at its earliest stage for getting maximum benefit from available treatment. In endocrine referral centers, the frequency of GHD is higher than in general clinics.

RECOMMENDATIONS

We can do screening for growth hormone deficiency selectively if a child had history of abnormal presentations, birth asphyxia, neonatal hypoglycemia and hyperbilirubinemia and features of midfacial crowding.

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ANNEXURE

PATIENT DATA FORM

Patient name:
Age / sex:
Endocrine no:
Address:

Date:
SE status:

CLINICAL HISTORY

SYNCOPE	**YES / NO**
CONSTIPATION	**YES / NO**
POLYUREA	**YES / NO**
FEVER / LETHARGY	**YES / NO**
SEIZURES	**YES / NO**
PRECOCIOUS PUBERTY	**YES / NO**
DEFORMITIES	**YES / NO**
TRAUMA	**YES / NO**
TREATMENT HISTORY	
FEATURES OF IINCREASED ICP	**YES / NO**
VISUAL DISTURBANCES	**YES / NO**

OBTRETIC HISTORY:

ANTENATAL HISTORY:

FEVER / RASHES	**YES / NO**
DRUG INTAKE	**YES / NO**
SPECIFY IF ANY	
MATERNAL ILLNESS	**YES / NO**
SPECIFY IF ANY	
ANTEPARTUM	**YES / NO**

HEMARRHAGE	
MODE OF DELIVERY	**NATURAL / LSCS /FORCEPS**
PRESENTING PART	**VERTEX / BREECH**
BIRTH WEIGT	
BIRTH ASPHYXIA	**YES / NO**
NEONATAL HYPERBILIRUBINEMIA	**YES / NO**

MATERNAL HISTORY:

PUBERTY AGE	
MATERNAL SMOKING / ALCOHOL	**YES / NO**

FAMILY HISTORY:

CONSANGUINITY	
FAMILY H/O SHORT STATYRE	

\

	FATHER	**MOTHER**	**SIBLING**
HEIGHT			
PERCENTILE			
PUBERTAL AGE			

MID PARENTAL HEIGHT	
DIETIC HISTORY	
ANTHROPOMETRY	**PERCENTILE CHART**
HEIGHT	
WEIGHT	
ARM SPAN	
UPPER SEGMENT	
LOWER SEGMENT	
US / LS RATIO	
HEIGHT AGE	

EXAMINATION:

MIDLINE DEFECTS	
GENITALIA	
CRYPTORCHIDISM	
HYPERPIGMENTED SKIN	
FUNDUS	
DENTAL EXAM	
BP	

HORMONAL STUDIES

THYROID PROFILE	**TSH**	**T4**	**T3**

CLONIDINE STIMULATION TEST	**BASAL**	**30 MINS**	**60 MINS**	**90 MINS**
GH LEVEL				

BLOOD INVESTIGATION : IGF1 level in serum

Sr.CORTISOL:

Sr.ACTH :

KARYOTYPING if indicated:

RADIOLOGY : X RAY FOR AGE

MRI SCAN.

INFORMED CONSENT FORM

I agree to participate in the study titled “Pattern of endocrine causes of short stature among children, 2-12 years of age in a urban referral centre”.

I confirm that I have been told about this study in my mother tongue (Tamil) and I had the opportunity to ask question. I confirm that I have been told about the risk and potential benefits of my child’s participation.

I understand that my child participation is voluntary and I may refuse to continue at any time without giving any reason if i think my child’s benefit is being affected.

I agree not to restrict the use of any data or results that arise from this study.

1. Name of the child :
2. Name of guardian/care giver :
   Signature :
   Date :
3. Name of the witness :
   Signature :
   Date :
4. Name of investigator :
   Signature :
   Date :

தகவல் தாள்

ஆய்வின் நோக்கம்

12 வயதிற்கு உட்பட்ட குழந்தைகளில் உயரக் குறைபாடு வருவதற்கான காரணம் மற்றும் இக்குழந்தைகளின் நோயின் தன்மைகளையும் அறிவதே இந்த ஆய்வின் நோக்கம்.

சட்டத்தினால் வழங்கப்பட்ட விவரம் இரகசியமாக பாதுகாக்கப்படும். இந்த ஆய்வில் தங்கள் குழந்தை பங்கேற்பது உங்களது விருப்பத்தைப் பொறுத்தது. இந்த ஆய்வில் இருந்து விலகுவதால் மருத்துவ சிகிச்சை அளிப்பதில் எந்தவித இடையூறும் நேராது. ஆய்வில் பங்கேற்கும் போது இடையில் விலகவோ, கேள்விகளுக்கு விடையளிக்காமல் இருக்கவோ தங்களுக்கு உரிமை உள்ளது.

ஆய்வு குறித்து தங்களுக்கு ஏதேனும் சந்தேகம் நேரிடின் ஆய்வாளரை நேரில் சந்திக்கவோ, தொலைபேசியில் தொடர்பு கொள்ளவோ வரவேற்கப்படுகிறீர்கள்.

அபாயங்கள் மற்றும் நன்மைகள்

இந்த ஆய்வில் பங்கேற்பதால் எந்தவித தீங்கும் ஏற்பட வாய்ப்பில்லை. இதில் பங்கேற்கும்போது செய்யப்படும் மருத்துவ பரிசோதனைகள் மற்றும் சிகிச்சை முற்றிலும் இலவசமானது.

ஒப்புதல் படிவம்

இந்த ஆய்வில் செய்யப்படுகின்ற செய்முறைகளினால் ஏற்படும் பக்க விளைவுகளுக்கு மருத்துவ உதவி செய்யப்படும். எந்தவித நஷ்ட ஈடும் தரப்படாமாட்டாது என்பதையும் அறிந்து கொண்டேன்.

1. நான் இந்த ---------- தேதியிட்ட தகவல் படிவத்தை நன்றாக படித்து, படித்துக் காட்டி எடுத்துரைத்ததை புரிந்து கொண்டேன். எனக்கு கேள்வி கேட்கும் வாய்ப்பும் கிடைத்தது.
2. இந்த ஆய்வில் நான் என்னுடைய சுய அறிவோடு பங்கு கொள்கிறேன். மேலும் இந்த ஆய்விலிருந்து எந்த வித காரணமும் தராமல் மருத்துவப் பரிசோதனையிலிருந்து நான் விலகிக் கொள்ளலாம். இதனால் சட்ட ரீதியான எந்த செயலும் உட்படுத்தாது.
3. Ethics குழுவின் அங்கத்தினர்களோ, இந்த ஆய்வை நடத்துபவர்களோ என்னுடைய மருத்துவ ஆய்வின் அனைத்து விவரங்களையும் என்னுடைய அனுமதியின்றி பார்க்கவோ, படிக்கவோ உரிமையுள்ளவர்களாவர். நான் இந்த ஆய்விலிருந்து விலகிக் கொண்டாலும் கூட என்னுடைய விவரங்களை அவர்கள் அறிந்து கொள்ள ஒத்துக் கொள்கிறேன். என்னுடைய விவரங்கள் அனைத்தும் 3வது நபருக்கோ அல்லது பத்திரிக்கையில் வெளியிடுவதற்கோ முயலமாட்டீர்கள் என நம்புகிறேன்.
4. இந்த ஆய்விலிருந்து பெறப்பட்ட புள்ளி விவரங்களையோ அல்லது முடிவுகளையோ பயன்படுத்தக் கூடாது என்று கட்டுப்படுத்த மாட்டேன்.
5. என் குழந்தையை இந்த மருத்துவ ஆய்விற்கு பங்கு கொள்ள பரிபூரணமாக சம்மதிக்கிறேன்.

கையொப்பம்.....தேதி.....

பெயர்.....

குழந்தையின் பெயர்.....

ஆய்வாளர் கையொப்பம் தேதி :

சாட்சிகள் கையொப்பம் தேதி :

ABBREVIATIONS

IGF	-	insulin like growth factor
$IGFBP_3$	-	insulin growth factor binding protein 3
GHD	-	growth hormone deficiency
GHRH	-	growth hormone releasing hormone
GH	-	growth hormone
hGH	-	human growth hormone
rhGH	-	recombinant growth hormone
FSS	-	familial short stature
CGD	-	constitutional growth delay
MPHD	-	multiple pituitary hormone deficiency